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Combination of Clinical Frailty Score and Myostatin Concentrations as Mortality Predictor in Hemodialysis Patients

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Objectives: Frailty is common among hemodialysis (HD) patients. Its assessment is usually based on clinical criteria. In the present work, we evaluated the interest of combining clinical frailty score and biomarkers to predict mortality of chronic HD patients. Four biomarkers were assessed: myostatin, insulin-like growth factor-1 (IGF-1), dehydroepiandrosterone sulfate (DHEA-S), and serum creatinine-to-cystatin C ratio (SCr/SCys).

Methods: Prevalent HD patients were enrolled from September 2016 to October 2017 in 2 centers in this observational prospective study and followed up for 5 years. Serum levels of myostatin, IGF-1, DHEA-S, and SCr/SCys were measured at baseline. Frailty was assessed using Fried frailty score (≥ 3 indicates frailty). The ability to predict 5-year mortality was assessed by calculating Cox regression analyses and areas under the curve (AUCs).

Results: We included 125 HD patients with the following characteristics: median age of 67 (53; 78) years, 40% of women, 41% of diabetics, and median dialysis vintage of 30 (16; 54) months. Among them, 46% were classified as "Frail" according to Fried score. Mortality rate at 5 years was 56%. The median follow-up was 49 (19; 60) months. Cox univariate analysis showed that higher age, frailty phenotype, and decreased concentrations of myostatin, IGF-1, DHEA-S, and SCr/SCys were associated with higher mortality. In multivariate analysis, only myostatin remained significant among the biomarkers. The AUC of Fried score and myostatin to predict mortality was significant and comparable: 0.72 (95% confidence interval [CI]: 0.63-0.80) and 0.72 (95% CI: 0.64-0.80), respectively. Combining myostatin with Fried score improved significantly the AUC (AUC = 0.79, 95% CI: 0.71-0.86) compared to Fried score alone or myostatin alone ($P = .0049$ and $P = .0035$, respectively).

Conclusion: Decreased concentrations of myostatin seem to be independently associated with higher risk of mortality. Combining Fried frailty score with myostatin concentration could improve the prediction of 5-year mortality in chronic HD patients.

Keywords: Frailty; hemodialysis; myostatin; biomarkers; mortality

Introduction

FRAILTY IS A syndrome initially described in geriatric patients and characterized by a loss of physiological state and increased vulnerability to stressors. It is associated with increased risk of adverse outcomes such as falls, hospitalizations, and mortality.[1] Recent studies have demonstrated that patients with end-stage renal disease or treated by hemodialysis (HD) present an increased risk of fragility at all ages.[2] The prevalence of frailty in end-stage renal disease or HD patients ranges from 29.6% to 81.5% among

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studies,[2,3] whereas in nondialysis chronic kidney disease patients, it ranges from 7.9% to 16%.[3,4] Frailty is usually assessed using clinical frailty scales that have demonstrated their ability to predict complications such as hospitalizations and mortality in HD patients.[5–10]

Moreover, some muscle mass biomarkers, such as insulin-like growth factor 1 (IGF-1) and myostatin, were able to detect muscle weakness in HD patients and correlated with mortality in previous studies.[11–13] The decreased level of dehydroepiandrosterone sulfate (DHEA-S), the main circulating androgen, was also identified as a predictor of mortality in HD patients.[14,15] This hormone plays an anabolic role in the muscle synthesis but also has multiple nonanabolic effects, including bone health and endothelial function with a potentially protective role against cardiovascular disease.[14,15] More recently, the serum creatinine-to-cystatin C ratio (SCr/SCys) was identified as an indicator of sarcopenia in HD patients.[16]

This study is based on part of the cohort from the Delanaye *et al.* study,[11] which evaluated the value of myostatin and IGF-1 in assessing muscle mass and predicting 1-year mortality of chronic HD patients. In this complementary study, we investigated the association of IGF-1 and myostatin but also 2 other biomarkers (DHEA-S and SCr/SCys) with mortality and suggested the interest of combining a clinical frailty assessment with relevant biomarkers to improve mortality prediction. Also, the follow-up period was extended to 5 years.

Methods

Population

The population has been already described.[11] Briefly, in this observational prospective study, we evaluated prevalent chronic HD patients. Patients were recruited in 2 dialysis centers from February 2016 to October 2017 and followed up for 5 years. The protocol was approved by the hospital Ethics Committee, conducted according to the standards of Good Clinical Practice and adheres to the Declaration of Helsinki. All patients signed an informed consent.

Demographic data of each participant were collected at baseline including age, sex, dialysis vintage, body mass index, smoking status, and primary cause of kidney failure. Comorbidities were also collected including diabetes mellitus, hypertension, acute myocardial infarction, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease (COPD), and active cancer. The age-adjusted Charlson Comorbidity Index (CCI) was evaluated for all patients. This index assesses comorbidity level by taking into account age and both the number and severity of 19 predefined comorbid conditions. The score obtained predicts survival at 1 and 10 years.[17] Finally, we assessed the Geriatric Nutritional Risk Index at baseline, which is a simple method to assess nutritional status based on body weight, height, and serum albumin.[18]

As this study was observational, no nutritional or exercise interventions specific to the study were carried out. Patients benefited from usual follow-up and interventions specific to their dialysis center.

Clinical Assessment of Frailty

For all patients, the 5-point score published by Fried et al. was calculated.[19] This score has 5 components: (1) unintentional weight loss, (2) physical inactivity, (3) slowness, (4) weakness, and (5) exhaustion. Weight loss was determined by a 5% weight loss over the past year based on the patient's medical records. If the information was not available, it was assessed by asking the patient. To avoid the influence of excess volume load among dialysis patients, we applied the dry weight of patients (after dialysis) to assess the weight loss. Physical inactivity was evaluated by the Minnesota Leisure Time Physical Activity questionnaire.[20] For slowness, participants walked at their usual pace over a 4.6 m course (15 ft). Weakness was evaluated by hand grip strength measured using a handheld dynamometer (JamarVR Hydraulic Hand Dynamometer, Model 5030J1, Patterson Medical, Warrenville, IL, USA). Participants performed 3 tests with dominant hand before the start of the dialysis session, and the higher value was used to determine frailty using cutoffs on the basis of sex and body mass index.[19] Exhaustion was on the basis of responses to questions about endurance and energy from the Center for Epidemiologic Studies depression scale.[21] Patients received a total of 0 to 5 points according to the number of these potential criteria that they met. Participants were classified as "not frail" (score < 3) or "frail" (score ≥ 3).

Measurement of Biomarkers

Samples were drawn at baseline from participants before the dialysis session. Samples were allowed to clot 30 minutes and then centrifuged at 45,000 rpm for 10 minutes. Sera were aliquoted and kept frozen at $-80°C$ until determination. IGF-1 was determined on the IDS-iSYS analyzer (IDS, Boldon, UK). In this chemiluminescent assay, the patient samples are incubated with an acidic solution to dissociate IGF-1 from the binding proteins, and 2 monoclonal antibodies are used to measure IGF-1. In our hands, the coefficient of variation (CV) was 7%. Myostatin was measured using an enzyme-linked immunosorbent assay from R&D (R&D Systems, Minneapolis, MN). According to the manufacturer, the myostatin assay measures the total form of the peptide (only the C-terminal form being bioactive). In our hands, the CV for this assay ranged from 7.2% to 8.9%. DHEA-S was measured by immunochemiluminescence on an Abbott Alinity analyzer and cystatin C was measured by turbidimetry with the Roche method on a cobas c501 instrument. The CV for DHEA-S was $< 5\%$ and for CysC, it was $< 4\%$. All these measurements were done in the same laboratory (Department of Clinical Chemistry, University of Liège) accredited for the ISO15189 Guideline.[22] Other biological parameters (hemoglobin, serum

calcium, phosphorus, parathyroid hormone, C-reactive protein, albumin, and serum creatinine [SCr]) were measured locally. Albumin was measured using Bromocresol green in all centers. Because parathyroid hormone was measured by different assays in the 2 centers, we considered relative results expressed in multiples of the upper normal limit values, as established by our team.[23]

Survival Analysis

The predictive value of the biomarkers and Fried score on all-cause mortality was studied with the 5-year survival data of follow-up.

Statistics

Results were expressed as mean and standard deviation when distribution was normal and as median with quartiles (quartile 1 and quartile 3) when not. Normality was assessed by the Shapiro-Wilk test. The qualitative variables were expressed as number and frequency (%).

Cox proportional hazard regression models were used to study the risk of 5-year mortality associated with frailty and biomarkers. Multivariate regression analysis was used to identify the factors associated with outcomes. Age, gender, and clinical and biological variables that were statistically significant in univariate analysis ($P < .05$) were tested.

The ability to predict mortality was assessed by calculating areas under the curve (AUCs) from the receiver operating characteristic (ROC) analysis. ROC curves were evaluated for Fried score and biomarkers of interest with death at 5-year follow-up as the classification variable. AUCs were compared by Hanley & McNeil test.[24] For these analyses, we also compared the combination of myostatin (logistic regression model) with Fried score.

Finally, univariate survival curves (Kaplan-Meier) were calculated for strata defined by the biomarker cutoff corresponding with the optimal Youden index, based on the ROC analysis.

Results

In total, 172 prevalent HD patients were recruited in the 2 centers. Five patients were excluded because of incomplete Fried score and 42 were excluded because biomarker concentrations were not available (Fig. 1). Demographics and biochemistry data at baseline for the total studied population (n = 125) are summarized in Table 1. Briefly, median age was 67 (53; 78) years, with 40% of women and 41% of diabetic patients. The median dialysis vintage was 30 (16; 54) months. Among them, 46% were classified as "Frail" according to Fried score. The median follow-up was 49 (19; 60) months. Median serum concentrations of myostatin, IGF-1, and DHEA-S were 3,622 (2,123; 4,624) pg/mL, 135 (88; 191) μg/L, and 1.75 (0.85; 3.57) μmol/L, respectively. The comparison of frail and nonfrail patients at baseline (Table 1) showed that frail patients were older and had more frequently a history of diabetes mellitus, cerebrovascular disease, acute myocardial infarction, peripheral vascular disease, COPD, and active cancer. Moreover, in frail patients, plasma concentration of hemoglobin, prealbumin, and SCr were significantly lower, whereas serum concentration of C-reactive protein was higher. The concentration of IGF-1, myostatin, DHEA-S, and SCr/SCys were also different in frail patients compared to "not frail" patients: 116 (76; 163) versus 151 (110; 201), 2,533 (1,729; 3,373) versus 3,877 (2,594; 5,221), 1.1 (0.6; 2.5) versus 2.25 (1.26; 4.07), and 1.2 (1.0; 1.4) versus 1.5 (1.3; 1.7), respectively. At the end of the follow-up period, 56% of the patients had died, 81% of whom were frail patients and 36% of whom were 'nonfrail' patients ($P < .0001$).

Mortality: Cox Proportional Hazards Models

During the 5 years of follow-up, 70 (56%) patients died, corresponding to 81% of "frail" patients and 35% of "not frail" patients ($P < .0001$). Cox proportional hazard models are presented in Table 2. Since the CCI takes into account different comorbidities, we used this tool for Cox analysis rather than comorbidities separately. The univariate Cox analysis revealed that age, smoking history, HD, CCI, and frailty by Fried score were all associated with higher mortality. Regarding the biological data, mortality was associated with decreased concentrations of albumin, prealbumin, myostatin, IGF-1, SCr, SCr/SCys, and DHEA-S. The first multivariate models included age, gender, and relevant clinical variables. In the second model, we included age, gender, and the relevant biomarkers. The third model included age, gender, and both the clinical and biological variables that were significant in model 1 and model 2. The different models revealed that when age and gender were included, only myostatin and SCr concentrations remained significant among the different biomarkers. In model 3 including clinical and biological variables, the "frail" status, CCI, and myostatin were still significant unlike SCr concentration.

Mortality: ROC and Survival Curves

The determination of frail status according to Fried was significant to predict mortality with an AUC of 0.72 (95% confidence interval [CI]: 0.63-0.80). Since myostatin was the only biomarker that remained significant for mortality prediction in Cox multivariate analysis, we only performed ROC curve analysis for this biomarker. Myostatin had a significant and comparable AUC compared to Fried score (AUC = 0.72; 95% CI: 0.64-0.80).

Combining by logistic regression myostatin with Fried score improved significantly the AUC (AUC = 0.79; 95% CI: 0.71-0.86) compared to Fried score or myostatin alone ($P = .0049$ and $P = .035$, respectively) (Fig. 2).

Based on ROC curve analysis, the most predictive cutoff value (Younden Index) for myostatin was 3077 pg/mL. In this cohort, myostatin concentrations less than 3,077 pg/mL were reported in 36 (63%) of "frail" patients and 25 (37%) of "not frail" patients, respectively.

We considered frailty and a myostatin concentration below the cutoff value as risk factors and classified patients into 4 groups based on those factors.

- Group 1: Frail and myostatin concentration below the cutoff value of 3,077 ng/mL (n = 36).
- Group 2: Frail and myostatin concentration over the cutoff value (n = 21).
- Group 3: Not frail and myostatin concentration below the cutoff value (n = 25).
- Group 4: Not frail and myostatin concentration over the cutoff value (n = 43).

Mortality rates in these subgroups were 94%, 57%, 48%, and 28%, respectively.

The third figure illustrates survival curves comparing subgroups.

When the cutoff value of myostatin was considered to divide patients into 2 groups, the survival curves calculated were significantly different ($P < .0001$) (Fig. 3B).

When comparing survival curves of patients from Group 1 with the rest of the cohort (not frail and/or myostatin concentration more than 3,077 pg/mL), the difference in survival was even more pronounced ($P < .0001$) (Fig. 3C). Finally, using the same myostatin cutoff value but within the 2 frailty subgroups, we observed a higher mortality in frail patients with lowered myostatin levels ($P = .002$) (Fig. 3D). Among nonfrail patients, a similar trend was observed, but it was not statistically significant ($P = .085$) (Fig. 3E). The comparison of survival curves of the 4 groups demonstrated a global P value $< .0001$ (Figure S1).

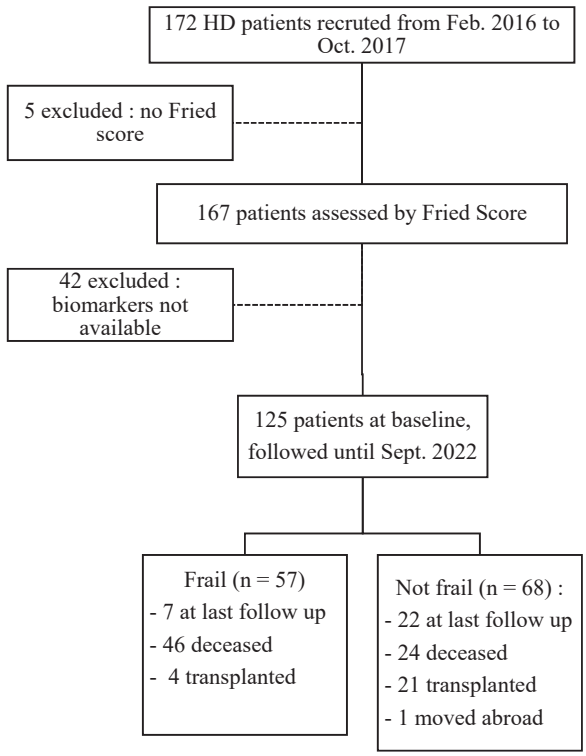

Figure 1. Flow chart of the study.

Discussion

Our investigation reports the interest of combining myostatin with frailty phenotype assessment to predict 5-year mortality in chronic HD patients. Myostatin was the only biomarker independently associated with an increased risk of mortality when adjusted for age, gender, and frailty phenotype.

The Fried score was first developed to define the phenotype of frailty in adults aged more than 65 years and to predict adverse outcomes such as falls, hospitalizations, and mortality based on data from the Cardiovascular Health Study.[19] This tool is the most widely used in studies of frailty in dialysis patients[25] and has demonstrated a strong association between frailty phenotype and all-cause mortality in this population.[7,26,27]

IGF-1 is a protein that activates muscle growth and repair. Therefore, the consequences of a decreased IGF-1 plasma concentration on muscle mass are simple to understand. Reduced levels of IGF-1 have been associated with cardiovascular disease and all-cause mortality in the general population.[28] The association with all-cause mortality has also been described in HD patients by Delanaye *et al.*, Jia *et al.*, and Nilsson *et al.* but with shorter follow-up duration.[11,12,29] In these 2 studies, the association remained significant in multivariate analysis including age and gender, which is not the case in our work.

Concerning the DHEA-S, it has been suggested that a reduced production of this androgen could partially explain age-related sarcopenia in general population since this biomarker is independently associated with muscle mass and muscle strength.[30,31] We could not find any study evaluating the association of DHEA-S with muscle mass or muscle function in chronic kidney disease (CKD) or HD patients. There are only 2 studies demonstrating an independent association between low DHEA-S plasma concentration and all-cause mortality for men in HD patients but it is not clear if DHEA-S plays a specific role or is just a reflection of overall health.[14,15] In our study, DHEA-S was not significant anymore for mortality when age and other biomarkers were included in multivariate Cox analysis.

Then, the SCr/SCys ratio was introduced more recently as an interesting indicator of sarcopenia in HD and nondialysis CKD patients.[16,32,33] Serum creatinine and Cystatin C are both markers of renal function but SCr is also well known to be positively correlated with muscle mass, while serum cystatin C is only slightly influenced.[33,34] Therefore, the SCr/SCys ratio has been proposed as an interesting tool for prediction of sarcopenia in patients with altered renal function. Recently, Jung *et al.* identified poorer survival in critically ill patients with acute kidney injury requiring continuous renal replacement therapy that presented a

Table 1. Demographic and Biochemistry Description of Cohorts

	All	Frail	Not Frail	
	n = 125	n = 57	n = 68	*P* Value
Age (y)	67 (53; 78)	72 (63; 81)	60 (43; 73)	.0001
Gender, % male	75 (60)	34 (60)	41 (60)	1
Dry weight (kg)	71.5 (60; 82.6)	71.0 (57.0; 84.1)	72.0 (60.5; 81.5)	.72
Height (cm)	167 ± 10	166 ± 11	168 ± 10	.37
BMI (kg/m^2)	24.4 (22.0; 29.0)	23.7 (21.4; 30.3)	25.2 (22.2; 28.9)	.52
Dialysis vintage (m)	30 (16; 54)	29 (16; 51)	31 (16; 58)	.52
Residual diuresis, % yes	81 (65)	34 (60)	47 (69)	.76
Kt/V	1.40 (1.30; 1.50)	1.40 (1.25; 1.50)	1.40 (1.30; 1.50)	.30
HDF	100 (80)	35 (61)	65 (98)	<.0001
Fried score	2 (1; 4)	4 (3; 4)	1 (0; 1)	<.0001
CCI	7 (5; 8)	8 (6; 9)	5 (4; 8)	<.0001
GNRI	98 (93; 102)	98 (93; 101)	98 (94; 104)	.47
Etiology of ESRD, %				
Diabetic nephropathy	30	40	22	.030
Renal vascular disease	18	19	18	.88
Glomerulonephritis	17	5	26	.0017
PKD	3	0	6	.06
Other	31	35	28	.40
Comorbidities, %				
Diabetes mellitus	41	53	31	.0013
Hypertension	86	89	82	.27
AMI	21	33	10	.0016
CVD	16	25	9	.016
PVD	22	32	15	.024
COPD	21	26	16	.17
Active cancer	6	10.5	3	.009
Smoking history	42	46	40	.5
Laboratory				
Hemoglobin (g/dL)	11.2 (10.3; 11.7)	10.8 (10.0; 11.4)	11.3 (10.4; 11.9)	.012
Ca^{2+} (mmol/L)	2.20 (2.08; 2.33)	2.25 (2.11; 2.35)	2.19 (2.08; 2.32)	.37
PO^{4-} (mmol/L)	1.59 (1.28; 2.05)	1.50 (1.28; 1.79)	1.79 (1.29; 2.15)	.10
Albumin (g/L)	38 (36; 41)	38 (36; 41)	38 (35; 41)	.63
Prealbumin (g/L)	0.29 (0.25; 0.33)	0.27 (0.22; 0.32)	0.30 (0.26; 0.35)	.0069
CRP (mg/L)	4.6 (2.2; 11.4)	6.5 (3.3; 16.0)	3.1 (1.4; 9.1)	.0011
Bicarbonates (mmol/L)	23 ± 3	23 ± 4	22 ± 3	.097
25-OH vitamine D	32 (19; 40)	36 (25; 42)	25 (16; 38)	.02
PTH (multiple of the upper limit)	5.5 (2.7; 8.5)	5.5 (2.4; 8.5)	5.4 (3.4; 8.3)	.42
Creatinine (mg/dL)	7.30 (5.80; 9.78)	6.80 (5.54; 8.52)	8.30 (6.01; 10.70)	.79
Cystatin C (mg/L)	5.72 ± 1.40	5.85 ± 1.44	5.60 ± 1.37	.0018
Creatinine/Cystatin C	1.3 (1.1; 1.6)	1.2 (1.0; 1.4)	1.5 (1.3; 1.7)	.31
IGF-1 (iSYS) (μg/L)	135 (88; 191)	116 (76; 163)	151 (110; 201)	<.0001
Myostatin (pg/mL)	3,622 (2,123; 4,624)	2,533 (1,729; 3,373)	3,877 (2,594; 5,221)	.0099
DHEA-S (μmol/L)	1.75 (0.85; 3.57)	1.1 (0.6; 2.5)	2.25 (1.26; 4.07)	.0007

AMI, acute myocardial infarction; BMI, body mass index; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVD, cerebrovascular disease; DHEA-S, dehydroepiandrosterone sulfate; ESRD, end-stage renal disease; GNRI, Geriatric Nutritional Risk Index; HDF, hemodiafiltration; IGF-1, insulin-like growth factor 1; PKD, polycystic kidney disease; PTH, parathyroid hormone; PVD, peripheral vascular disease.

Results are Expressed as Mean and Standard Deviation (SD) When Distribution was Normal and as Median With Quartiles [Quartile 1 and Quartile 3] When Not.

lower SCr/Scys ratio.[35] In our work, decreased SCr/SCys was associated with increased mortality in univariate analysis but it did not remain significant in multivariate analysis.

Finally, myostatin is a protein belonging to the transforming growth factor β family and is mostly secreted by mature muscle cells. Its role is to limit overgrowth of muscles cells, thereby preventing excessive muscle mass development and leading to a controlled reduction in muscle size.[36] Its inhibiting effect has been evaluated in both experimental models and clinical studies, reporting increased concentrations of myostatin in age-associated sarcopenia and an inverse association with muscle mass in chronic diseases such as COPD or human immunodeficiency virus infection.[37-40] Interestingly, in HD patients, several studies have demonstrated a positive correlation between myostatin concentration and muscle mass and strength

Table 2. Association Between Clinical Data, Biomarkers of Interest Concentrations, and 5-Year Survival: Cox Proportional Hazard Models (n = 125)

Univariate Analysis	HR	95% CI	*P* Value
Age	1.06	1.04-1.09	<.0001
Gender	1.31	0.81-2.14	NS
HD	0.41	0.25-0.69	.0007
Smoking history	1.65	1.03-2.64	.0372
CRP (mg/dL)	1.006	0.999-1.012	NS
Albumin	0.946	0.899-0.995	.0322
Prealbumin	0.001	0.00-0.04	.0002
SCr (mg/dL)	0.91	0.83-0.99	.0266
IGF-1 (mcg/L)	0.9926	0.9885-0.9967	.0005
Myostatin (pg/mL)	0.9996	0.9994-0.9998	<.0001
SCr/SCys	0.26	0.13-0.52	.0001
DHEA-S (μmol/L)	0.74	0.63-0.87	.0003
Frail status (fried ≥ 3)	3.73	2.27-6.14	<.0001
CCI	1.43	1.29-1.58	<.0001
GNRI	0.98	0.95-1.01	.1294
Multivariate models			
Model I			
Age	1.04	1.0104-1.0614	.0053
Gender	1.09	0.6511-1.8351	NS
HD	1.16	0.6399-2.1116	NS
Smoking history	1.35	0.8140-2.2272	NS
CCI	1.23	1.0798-1.3981	.0018
Frail status (fried ≥ 3)	2.50	1.4178-4.4083	.0015
Model II			
Age	1.05	1.03-1.08	<.0001
Gender	1.60	0.93-2.77	NS
Albumin	0.95	0.89-1.01	NS
Prealbumin	0.043	0.0004-4.512	NS
SCr (mg/dL)	1.22	1.04-1.44	.0133
IGF-1 (mcg/L)	0.999	0.995-1.004	NS
Myostatin (pg/mL)	0.9997	0.9994-0.9999	.0015
SCr/SCys	0.37	0.11-1.25	NS
DHEA-S (μmol/L)	0.9	0.75-1.09	NS
Model III			
Age	1.03	1.01-1.06	.0137
Gender	1.07	0.63-1.81	NS
CCI	1.25	1.1-1.42	.0008
Frail status (fried ≥ 3)	1.88	1.01-3.24	.0231
SCr (mg/dL)	1.11	0.98-1.26	NS
Myostatin (pg/mL)	0.9997	0.9995-0.9999	.003

CI, confidence index; CCI, Charlson Comorbidity Index; CRP, C-reactive protein; DHEA-S, dehydroepiandrosterone sulfate; GNRI, Geriatric Nutritional Risk Index; HD, hemodialysis; HR, hazard ratio; IGF-1, insulin-like growth factor 1; NS, not significant; SCr, serum creatinine; SCys, serum cystatin C.

Model 1: Age, gender, and clinical variables that were significant in univariate analysis.

Model 2: Age, gender, and biological variables that were significant in univariate analysis.

Model 3: Age, gender, and variables that were significant in model 1 and 2.

which is rather contradictory considering the mechanism of action.[11,41,42] Patients with CKD or those undergoing HD have higher plasma concentrations compared to the healthy population.[43,44] However, the underlying pathophysiology in this specific population is not well understood. This increase seems to be the consequence of impaired renal clearance rather than overproduction.[36] Only hypothesis have been proposed to explain this correlation. First, there are multiple other factors in these patients that negatively influence muscle mass: physical inactivity, malnutrition, uremic toxins, and inflammation. These factors also influence myostatin secretion.[11,43] Then, myostatin abundance may not reflect the activity as it is secreted as a precursor that needs cleavage to liberate its mature biological form.[45] Finally, myostatin is produced by mature muscle cells and therefore its concentration might just be a reflection of muscle mass and function.[11,13,43] In our study, plasma concentrations of myostatin were significantly lower in frail patients ($P < .0001$) than in nonfrail group. In all Cox proportional hazard models, myostatin remained significant for assessing the risk of mortality. Sakashita *et al.* recently published similar data

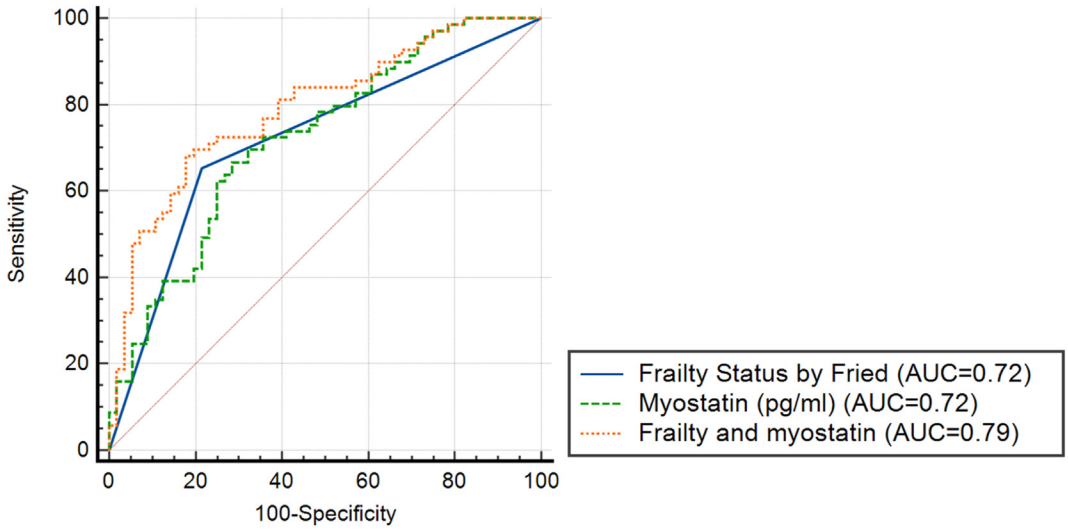

Figure 2. ROC curves for Fried score, myostatin, IGF-1, DHEA-S, and serum creatinine to serum cystatin ratio to predict mortality at 5 years (unadjusted). DHEA-S, dehydroepiandrosterone sulfate; IGF-1, insulin-like growth factor 1; ROC, receiver operating characteristic.

studying 1-year mortality in HD patients.[13] They reported an AUC of 0.85 in ROC curve analysis for 1-year mortality with myostatin, while in our study, AUC was 0.72 with this biomarker when assessing 5-year mortality. The combination of frailty assessment and myostatin improved significantly the mortality prediction and reached an AUC of 0.78. The ROC curve analysis for 5-year mortality using myostatin as a binary variable (over or below the cutoff value of 3,077 pg/mL) showed an AUC similar to myostatin as a continuous variable. Like we demonstrated with myostatin as a continuous variable, the combination of myostatin concentration less than or more than 3,077 pg/mL with the frailty assessment by Fried improved significantly the mortality prediction compared to Fried score and myostatin alone ($P = .0031$ and $P = .0134$, respectively). Regarding the Kaplan-Meier survival curves using the same cutoff value, decreased levels of myostatin were associated with a higher mortality in the whole cohort and it remained significant when only considering the frail patients. For nonfrail patients, we could only observe a trend but it was not significant in this subgroup.

Although this was not the initial aim of this work, which focused on frailty, CCI also demonstrated a good prediction of 5-year mortality, with an AUC of 0.84 (95% CI: 0.76-0.90). The association of CCI with myostatin by logistic regression was significantly better than CCI or myostatin alone ($P = .03$ and $P = .0002$, respectively) (see Figure S2).

Fried's assessment, CCI, and myostatin all remained significant when combined in the same multivariate model. This suggests that they provide independent elements in prediction of mortality. Indeed, Fried score corresponds to an assessment of physical capacity (potentially progressive and modifiable), whereas the CCI is based solely on the patient's medical history.

There are limitations to our study that should be noted. First, the sample size is limited with patients included from only 2 Belgian dialysis centers. Looking at comorbidities, it was noted that 8 patients presented active cancer and were unevenly distributed between the frailty groups. Frail patients presented a higher level of active cancer patients (10.5% in frail patients compared to 3% in "nonfrail" patients, $P = .009$). When those 8 patients were excluded of the Cox multivariate analysis and Kaplan-Meier survival curves, it did not change the conclusions of the analyses (data not shown).

Second, biomarkers were only measured once at baseline. Further studies are needed to realize repeated measures and assess their evolution in this population. Then, there is no standardization for the measurement of myostatin and IGF-1 plasma concentrations which limits the comparison of our data with other studies. Also, the enzyme-linked immunosorbent assay–based approach used for the measure of myostatin has limitations as it measures the whole protein which does not necessarily reflect myostatin's bioactivity.[46] Finally, this study is only observational which does not allow to draw conclusions in regards to causality.

In conclusion, this study suggests that combining Fried frailty score with myostatin concentration improves the prediction of 5-year mortality in chronic HD patients. Myostatin seems to be of interest as this biomarker was independently associated with all-cause mortality.

Practical Application

This work highlights the interest of the myostatin biomarker in improving mortality prediction. Further studies are needed to evaluate the effect of implementing measures to limit the complications of frailty in patients identified as being at high risk of mortality.

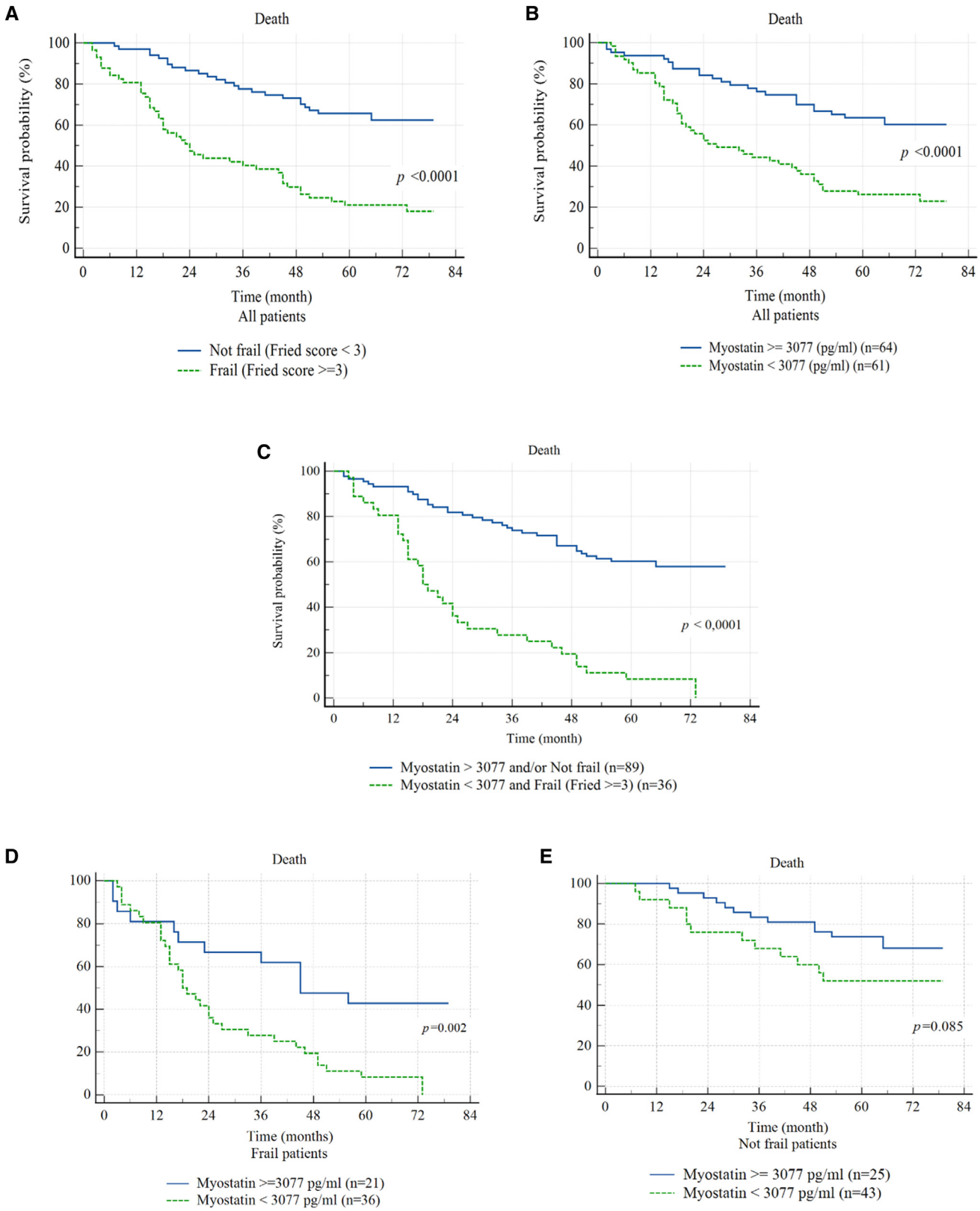

Figure 3. Survival curve for frailty phenotype by (A) Fried score, (B) myostatin, and (C) the association of a frailty phenotype with a myostatin below the cutoff value in the whole cohort. Within subgroups of frailty, (D) myostatin in frail patients and (E) nonfrail patients.

Disclosure

The results presented in this article have not been published previously in whole or part, except in abstract.

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The authors declare that they have no relevant financial interests.

CRediT Authorship Contribution Statement

Sophie Cornet: Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Kevin Quinonez:** Conceptualization, Methodology, Investigation. **Xavier Warling:** Investigation, Supervision, Writing – review & editing. **François Jouret:** Supervision, Writing – original draft. **Antoine Lanot:** Data curation, Writing – review & editing. **Olivier Bruyère:** Formal analysis, Data curation, Supervision, Writing – original draft, Writing – review & editing. **Etienne Cavalier:** Conceptualization, Methodology, Investigation, Resources, Writing – original draft, Funding acquisition. **Pierre Delanaye:** Conceptualization, Methodology, Investigation, Formal analysis, Supervision, Writing – original draft, Writing – review & editing, Project administration, Funding acquisition.

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Supplementary Data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1053/j.jrn.2025.01.005.

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